PATENT

Attorney Docket No. 29666/35415

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Williams *et al.*

Serial No. 09/529,053

Filed: April 6, 2000

For: Anti-Viral Uses of Leflunomide Products

Group Art Unit: 1617

Examiner: S. Wang

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June 26, 2003

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APPLICANTS' REPLY AND DECLARATIONS OF W. JAMES WALDMAN, Ph.D. AND EDWARD S. MOCARSKI, JR., Ph.D. UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

This reply is in response to the Office Action dated February 26, 2003, wherein all pending claims (16-25) were rejected under 35 U.S.C. §103(a). Attached hereto as Exhibit 1 is a copy of the pending claims.

REMARKS

I. Rejections of Claims 16-25

Claims 16, 17, 19, 20, 21, 24, and 25 were rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by the disclosures of Weithmann *et al.*, U.S. Patent No. 5,556,870 (hereafter "Weithmann") in view of Flamand *et al., J. Virol., 65:*5105-5110 (1991) (cited as CAPLUS Abstract, AN 1991:581163) (hereafter "Flamand") and, with respect to all claims listed above except for claim 19, in view of Hammer, *AIDS,* 10:suppl. 3, s1-s11 (1996) (hereafter "Hammer"). It was the Examiner's position that:

Weithmann *et al.* teach a method of treating disorder in which interleukin 1 beta is involved. The disorders includes viral infections, such as HIV or hepatitis, comprising administering leflunomide to the patient. *See*, particularly, the abstract and the claim. The dosage may range from 3-50 mg daily, but may be higher if required. *See*, particularly, column 3, lines 7-16.

Weithmann *et al.* does not teach expressly the amount effective to inhibit viral virion assembly. However, the optimization of a result effective parameter, e.g., effective amount for a therapeutical dosage of a known therapeutical agent, is considered within the skill of the artisan. *See*, *In re Boesch and Slaney*, (CCPA) 204 USPQ 215. Further, treating a disease with an agent in a host would lead the agent contacting the pathogenic cell. A method known to be useful for treating viral infection would have been reasonably expected to be useful for prophylactic purpose. Further, known antiviral agents would have been reasonably expected to be effective *in vitro* against virus. Finally, since leflunomide is effective against virus through different mechanism, it would have been reasonably expected to effective against those virus with resistance to antiviral agent that inhibit viral DNA replication (emphasis supplied).

Claims 16, 17, 20, 21, 24 and 25 were rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by the disclosures of Coghlan *et al.*, WO 94/24095 (hereafter "Coghlan") in view of Applicant Williams and his co-workers in McChesney *et al., Transplantation, 57:*1717-1722 (1994) (hereafter, "McChesney"). It was the Examiner's position that:

> Coghlan *et al.* teaches compounds with structures and biological activity closely related to leflunomide or its active metabolite. *See*, particularly, the abstract, page 2, the examples and the claims. These compounds are known to be useful for treating or preventing viral infection such as hepatitis and cytomegalovirus infection. *See*, page 4, lines 23-32.
>
> Coghlan *et al.* does not teach expressly the employment leflunomide or its metabolite, or the particular amount herein for administration.
>
> However, McChesney *et al.* teaches that both leflunomide and A771726 are known to be effective in preventing viral infection. *See*, particularly, the abstract at page 1717, and the materials and method at page 1717-1718.
>
> Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to employ the compounds taught by Coghlan *et al.*, including both

leflunomide and A771726, for treating or prevention of viral infections such as hepatitis and CMV.

A person of ordinary skill in the art would have been motivated to employ the compounds taught by Coghlan *et al.*, including both leflunomide and A771726, for treating or prevention of viral infections such as hepatitis and CMV because these compounds are known to be useful for treating or preventing viral infection, and both leflunomide and A771726 are known to be similarly useful as the other compounds. Further, known antiviral agents would have been reasonably expected to be effective *in vitro* against virus. Finally, since leflunomide is effective against virus through different mechanism, it would have been reasonably expected to effective against those virus with resistance to antiviral agent that inhibit viral DNA replication.

Claim 19 was rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by Coghlan in view of McChesney and Flamand.

Claims 22 and 23 were rejected under 35 U.S.C. §103(a) as assertedly rendered obvious by Coghlan in view of McChesney and Hammer.

II. Grounds for Reconsideration

A. Regarding the Section 103(a) Rejection
Based on Weithmann, Flamand and Hammer

Applicants submit that no *prima facie* case of obviousness of the claimed subject matter can properly be made out through application of the primary (Weithmann) and secondary (Flamand and Hammer) references. *See*, W. James Waldman Declaration ("Waldman Declaration") attached hereto as Exhibit 2.

Weithmann does not establish that any leflunomide product was known in the art to be useful as an "anti-viral agent" or to be "effective against virus" or to be capable of inhibiting viral replication as claimed. Rather, Weithmann at best asserts only that *in vitro* tests of un-metabolized leflunomide (HWA 486) suggest activity in modulating the *in vivo* secretion of IL-1β by cells in patients having any number of diseases, including viral infections. (*See* Waldman Declaration, specifically Paragraph 5)

Weithmann states that leflunomide (HWA 486) is rapidly metabolized upon administration to form an active metabolite (A771726) (column 1, lines 9-37) but then

observes that leflunomide, but not its metabolite, has activity in inhibiting cytokine "synthesis and liberation" (*See* Column 1, lines 45-49). Weithmann then "demonstrates" *in vitro* an IL-1β reduction effect in a specially-prepared isolated blood cell fraction which was designed with a reduced capacity to metabolize leflunomide (*See* Example 1 and column 3, lines 23-26), but never addressed how to provide the special *in vitro* test conditions *in vivo*, i.e. how to prevent leflunomide from being metabolized promptly upon administration. In contrast, Applicants exemplify antiviral effects of leflunomide products, including reduction of viral load in a human, with leflunomide's metabolite, A771726 (*See* particularly Examples 5 and 8C of the Application). Contrary to the position taken by the Examiner, treatment with leflunomide is not established by Weithmann as "a method know to be useful for treating viral infection" (*See* Waldman Declaration, specifically Paragraphs 4 and 5).

The claims pending in the application all require inhibiting viral virion assembly, an element not disclosed or assertedly obvious from Weithmann in view of Flamand and Hammer. One skilled in the art would not expect that an innumosuppressive drug proposed to be capable of modulating IL-1β secretion in patients with various disorders would also be capable of inhibiting the assembly of the viral virion components. In fact, it would have been counter-intuitive for one skilled in the art to expect an immunosuppressive/anti-inflammatory agent to perform as an anti-viral agent, as it is well documented that agents with anti-inflammatory properties (such as modulating IL-1 β secretion) enhance prospects for developing viral disease (*See* Waldman Declaration, specifically Paragraphs 6-11).

It follows that no *prima facie* case of obviousness can be made out through combination of the Weithmann "teachings" with the disclosures of the secondary references Flamand (addressing IL-1β production by virally-infected cells) or Hammer (addressing pyridinyl compounds as anti-retroviral agents) because: (1) the primary Weithmann reference contains no suggestion of the anti-viral properties of leflunomide products as claimed by the Applicant, nor did the knowledge generally available to one of ordinary skill in the art at the time of filing suggest the modification of the references or to combine the teachings; (2) there is no reasonable expectation shown in the art for success of using leflunomide products as claimed;

and (3) the references alone or in combination do not teach all the limitations of the claims.

B. Regarding the Section 103(a) Rejection
Based on Coghlan and McChesney

One of ordinary skill in the art would not find the disclosures of the Coghlan reference alone or in combination with those of McChesney sufficient to support a *prima facie* case of obviousness for the Applicant's claimed subject matter.

Coghlan addresses the synthesis of compounds "having immunomodulatory activity" (page 1, line 6-7) and lists disease states assertedly treatable with such immunomodulatory agents (page 3, line 1 - page 4, line 30). This list includes virtually every conceivable illness having a direct or indirect immunological component and concludes with reference to a few viral diseases. Not one single scientific publication is cited for a showing of efficacy of leflunomide or structurally related isoxazoles in any of the disease states listed. The sole assay for biological activity (Example 295) is a mixed lymphocyte test, having no connection whatsoever to the assessment of anti-viral activity. Coghlan does not teach that isoxazole compounds structurally related to leflunomide products inhibit viral replication as claimed by Applicants.

Likewise, one of ordinary skill in the act would not find McChesney sufficient to support a *prime facie* case of obviousness, alone or in combination with Coghlan. The Examiner states, "McChesney *et al.* teaches that both leflunomide and A77 1726 are known to be effective in preventing viral infection." As confirmed in the Declaration of Edward S. Mocarski ("Mocarski Declaration") attached hereto as Exhibit 3, the Examiner's position is simply not supported by the reference.

McChesney evaluates the immunosuppressive effects of leflunomide alone and in combination with cyclosporine in dogs undergoing kidney allograft transplantation. The only mention in McChesney of viral infection is a statement in the abstract that, "Even at a high dose of 16mg/kg/day no viral or bacterial infections were noted." There is nothing reported in the article to support or explain this statement, which would be necessary in order to attribute the cause for such an observation to the administered drugs (*See* Mocarski Declaration, specifically

Paragraph 5). Moreover, it is not surprising that McChesney noted this lack of viral infection. Institutional animal care guidelines (followed by McChesney according to page 1721) require full vaccination of animals (*See* Mocarski Declaration, Paragraph 5).

Because the McChesney reference includes no experimental procedures for assessing antiviral or antibacterial effects of leflunomide, it cannot properly be held to teach the use of leflunomide products for inhibiting viral replication.

Clearly then, the Coghlan and McChesney references alone, or in combination, provide the skilled worker with no hint whatsoever that leflunomide products had been found to be effective in inhibiting viral replication or might be tested for such effects with any reasonable expectation of success.

III. Conclusion

The foregoing is believed to establish that claims 16-25 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

Date: June 26, 2003 By: _____

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EXHIBIT 1

ORIGINAL CLAIMS 1-15 (CANCELLED)

PENDING CLAIMS:

--16. A method for inhibiting viral replication in cells susceptible to viral infection comprising contacting said cells with a leflunomide product in an amount effective to inhibit viral virion assembly.

17. The method of claim 16 wherein the leflunomide product is N-(4-trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide (HWA 486).

18. The method of claim 16 wherein the leflunomide product is N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamde (A771726).

19. The method of claim 16 wherein the virus is a herpesvirus.

20. The method of claim 16 wherein the virus is selected from the group consisting of paramyxoviruses, pricornaviruses and hepatitis viruses.

21. The method of claim 16 wherein the virus is selected form the group consisting of CMV, HSV, measles virus, rhinoviruses, hepatitis B and hepatitis C.

22. The method of claim 16 further comprising contacting the cells with another anti-viral agent.

23. The method of claim 16 further comprising contacting the cells with a pyrimidine.

24. The method of claim 16 wherein the virus is resistant to anti-viral agents that inhibit viral DNA replication.

25. The method of claim 16 wherein cells are virally infected.--